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Complementary Therapy with *Zingiber officinalis*

Clinical Cases

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Abstract

The application of *Zingiber officinalis* (ginger) root extract as a complementary therapy for several pathological conditions, and its major use in current western medicine has been described, as well as its common application in Traditional Chinese Medicine.

The phytochemical characterization of the natural active compounds present in ginger reflects its major healthy actions, and allows the perception of its several mechanisms of action on several pathologies.

Owning several chemical constituents with strong and assessed properties, a fourteen-day case study trial was performed using ginger root powdered capsules in order to evaluate its anti-inflammatory effect and compare it with a commonly prescribed non-steroidal-anti-inflammatory drug (ibuprofen) on patients suffering from chronic muscular pain, through the collection of subjective data provided throughout the study.

Keywords: *Zingiber officinalis*, Traditional Chinese Medicine, complementary medicine, ibuprofen, NSAIDs, anti-inflammatory, mechanisms of action, muscular pain.

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List of Abbreviations

ACh - Acetylcholine
ALT – *Algor Laedens Theory*
ASM – Airway Smooth Muscle
BP – Blood Pressure
CCBs – Calcium Channel Blockers
CNS – Central Nervous System
COX - Ciclooxygenase
CPR – C-Reactive Protein
DMSO – Dimethyl Sulfoxide
EC_{50} – Half-maximal effective concentration
GI – Gastro Intestinal
IL - Interleukin
IP - Intraperitoneal
LDL – Low Density Lipoprotein
LKs - Leukotrienes
LOX - Lipooxygenase
MIC – Minimum inhibitory concentration
mRNA – Ribonucleic Acid messenger
NF – Nuclear-Factor kβ
NO – Nitric Oxide
NSAID – Non Steroidal Anti-inflammatory drug
OA - Osteoarthritis
PDE – Phosphodiesterase
PGE_2 – Prostaglandin E2
PLC – Phospholipase C
Po – Pulmonary orb
TCM – Traditional Chinese Medicine
TNF – Tumour Necrosis Factor
TXB_2 – Thromboxane B2
VLDL – Very Low Density Lipoprotein

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Introductory Note

The terminology used in Traditional Chinese Medicine is based on the extensive work of Professor Manfred Porkert (Porkert, M. 1983), and is adopted in the Masters Degree of Traditional Chinese Medicine at Biomedical Sciences Institute of Abel Salazar, University of Porto.

Chapter I - Introduction

The support of the Plant Kingdom goes back to ancient times, practically inserted in all types of cultures and civilizations, as a medicinal, nutritional, cultural and aesthetical source, described in several ancient manuscripts, as for example the Bible, in which plants were designated as "*creators offers*", and seen with great respect and amazement (Hoareau & Da Silva, 1999).

The great incidence of aromatic plants in China and India lead to the extraction of essential oils, whose application in ointment preparations and balms had cosmetic goals (D'Amelio, 1999).

The rhizome of *Zingiber officinalis* is one of the most widely used species of the ginger family (*Zingiberaceae*) and is a common condiment for various foods and beverages. Ginger has a long history of herbal medicinal use dating back 2,500 years in China and India for the treatment of conditions such as headaches, nausea, rheumatism, nervous diseases, toothache, constipation, diabetes and colds. Characterized in Traditional Chinese Medicine as spicy and hot, ginger is claimed to warm the body and treat cold extremities, improve a weak and tardy pulse, address a pale complexion, and strengthen the body after blood loss which reflect its popularity and common use as a spice and medicinal plant (Ali, B. *et al*., 2008).

In Europe, ginger was firstly listed in *Galen's pharmacopoeia*, and was mentioned by *Plinius* the Elder for medicinal use. Since then, ginger has been part of the folk medicine and popular nutraceuticals (Bartels, E. *et al*., 2015).

Regarding Traditional Chinese Medicine, a considerable percentage of chronically ill patients (60-80%), regularly complaining about chronic pain, search for help in complementary medicine, however, in many places, this kind of medicine is not a major part of medical formation. For instance, in Germany, homeopathic and phytopharmacological treatments have strong traditions, whereas in other European countries Phytopharmacology has almost been abolished and even homeopathic treatment is sometimes close to being forbidden for irrational reasons (Greten, H., 2010). So, it is of great consideration to try to integrate TCM in the European western medicine in a complementary controlled manner.

The latest scientific developments have allowed the attendance of basic needs (nourishment, health and clothing) in a great part of the constantly growing human

population (Galembeck, F. & Csordas, Y. 2010; Gediya *et al*., 2011). Furthermore, the "Phytocosmetics" actually represents a sector in clear development, not only due to the scientific investigation growth, but also due to the real benefits of the application of plant products instead of some synthetic ones, as well as nowadays society requirements on adopting economical, ecological and safe production technologies, which in turn require a huge effort by investigators in finding distinct, natural and competitive compounds (Draelos, Z., 2001; Kole *et al*., 2005).

Currently, ginger is one of the most popular herbal medications for rheumatic and muscular diseases, and its beneficial effects have been previously and continuously described. Ibuprofen is usually prescribed as a pain killer in case of inflammations, e.g. muscular pain, teeth pain, headaches, menstrual pain and other kinds of pain, however many patients use this kind of medication (NSAIDs) for prolonged periods rather than the suitable time of treatment, and are unaware of the hazards this may imply due to serious gastric adverse manifestations (Bliddal, H. *et al*., 2000).

Despite the several healthy actions ginger has on the human body, chronic muscular pain has not been extensively reviewed, so it is of great importance to evaluate the efficacy of ginger root powdered capsules on the relief of chronic muscular pain on the leg, and to compare it with ibuprofen, a commonly prescribed NSAID, known to have several side effects, mainly stomach pain.

In this context, the aim of the present study was to assess the anti-inflammatory efficacy of ginger root powdered capsules provided from Solgar®, certificated manufacturers of multivitamin supplements since 1947 (through the evaluation of subjective data) and its tolerability, and compare it to one of the most commonly prescribed drugs for muscular pain - ibuprofen, known to be reasonably efficient and owning side effects.

Chapter II – Health impact – clinical case: comparison of commonly used NSAID – ibuprofen - with ginger root powdered capsules on chronic muscular pain

Summary

Background: The seek for alternative therapies has been extensively increasing by patients with chronic muscular pain, but only few of these drugs have been tested in a controlled manner, so the aim of the present study was to compare the efficacy and tolerability, both subjectively, of one commonly prescribed drug for muscular pain - ibuprofen (NSAID) - and ginger root powdered capsules provided from Solgar®, certificated manufacturers of multivitamin supplements since 1947, being ginger one of the most popular and versatile of herbal medications.

Design: the design was a randomised, fourteen-day controlled double-blind study. A placebo group (N=3) was included, with volunteers receiving sugar tablets twice a day for two weeks, a ginger root powder group (N=3) receiving 450mg of ginger root powdered capsules twice a day during 14 days, and finally, an ibuprofen group (N=3) receiving 400mg of ibuprofen twice a day during the fourteen-day trial. The main outcome measures were none to slight/moderate or total pain relief evaluation on days 1, 7 and 14, as well as subjective reports on adverse events. Ginger extract capsules were compared to placebo and ibuprofen in patients with chronic muscular pain in the legs. The study was conducted in accordance with Good Clinical Practice (European Guideline for GCP).

Results: the follow up was possible in all volunteers. A ranking of efficacy of the 14-day treatment trial resides on the following sequence: ibuprofen > ginger > placebo. In each active treatment group, all volunteers experienced slight to moderate improvements in muscular pain relief, having 1/3 of the volunteers treated with ibuprofen exhibited stomach pain as a side effect. The period of treatment showed a better effect of both ibuprofen and ginger root powdered extract than placebo. There were no serious adverse events reported during the entire period of treatment regarding the active medications, unless some changes in stool consistency and nausea (none of them severe), having only 1/3 of the volunteers taking ibuprofen reported uncomfortable stomach pain.

Conclusions: ginger root powdered capsules may be recommended for the relief of muscular pain, exhibiting less side effects when compared to commonly prescribed NSAIDs (e.g. ibuprofen). Further research on this potential activity of ginger is required, as well as a larger number of participants.

Subjects and Methods

Subjects

After signing an informed consent form, 9 volunteers were selected for the study and told to leave current medication for a week, in order to settle the beginning of this trial the week after. Patients over 30 years of age and under 70 were eligible for the study. During the study, all patients accepted to reach the culmination of the treatment period. Exclusion criteria included rheumatoid arthritis, dementia, neurological disorders and severe medical diseases, as well as no injections in muscles/joints were accepted within six months before the study.

All patients had complaints of pain due to excessive muscular use (e.g. excessive exercise in gyms), or due to a sedentary lifestyle (e.g. too much time sitting at the computer) or even farming.

Ginger root powdered extract

An extract of selected chinese ginger (*Zingiber officinale* – Ginger root extract) with a standardized content of ginger root powdered extract, owning 15 mg (5%) of ginger phenols, was used. The extract was formulated in soft capsules containing hydroxypropylmethyl cellulose, which shields the content of ginger.

Design

The trial was conducted in a double-blind controlled study, recruiting 9 volunteers complaining about muscular pain. At study entry, treatment with analgesics, NSAIDs and other drugs was stopped for a one-week washout period. The patients were then randomized to each treatment groups, with either 450 mg of ginger root powdered extract, 400 mg of ibuprofen or placebo (saccharine tablets). No further washout period was used between the 14-day period of study. The patients were randomized in blocks of three, a placebo group of volunteers (N=3), receiving saccharine tablets twice a day for fourteen days, a ginger root group (N=3) receiving 450mg of ginger root powdered capsules twice a day during 14 days, and finally, an ibuprofen group (N=3) receiving 400mg of ibuprofen tablets twice a day during the fourteen-day trial fully described in Table 1, all done under supervision. The study was conducted in accordance with the Good Clinical Practice (European Guidelines for GCP) at Farmácia Diniz Gomes, where patients regularly go for

medication supply and where they seek for health advice. No further washout period was used between the 14-day period of study.

Table 1 – Study design.

Active Medication	Dose	Formula	Duration of effect
Ginger root powder	450mg of standardised ginger root powder extract	capsules	Twice a day for 14 consecutive days
Ibuprofen	400mg	tablets	
Placebo (saccharine tablets)	≈ 4,4g (teaspoon of sugar)	tablets	

Masking

Both the ginger root extract powdered capsules and the ibuprofen tablets were indistinguishable for each patient, and as long as it was intact, the capsule did not release any smell or taste of ginger. Additionally, there was no difference in compliance as judged from capsule and pill consumption during the entire treatment period.

Assessment of efficacy (Outcome measures)

At the end of each treatment period, the main outcome measures were none to slight/moderate or total pain relief evaluation on days 1, 7 and 14, as well as subjective reports on adverse events. During each day of evaluation (1, 7 and 14-day of trial) each patient was requested to perform a clinical diagnosis through the fulfilment of a clinical case sheet, provided from Greten, H. (2010) in Traditional Chinese Medicine classes, which are fully filled (taking into account every detail referred from the patients along the trial) on the appendix. Finally, the intake of all trial medications was counted at each visit in the presence of the patients.

Assessment of safety

All adverse episodes, including changes in taste, were pointed out throughout the study.

Results

Demographics and Compliance

A total of 9 patients were evaluated, eligible and randomized for the treatment trial. All the patients complied with the prescheduled study-visits. Of the 9 patients, 3 were men and 6 women, 6 had primarily muscular pain due to hard farming, and 3 complained about muscular pain due to excessive exercise. The mean age of the patients was 42,4 (range between 30-70 years), and the mean duration of muscular pain was 2 weeks. Most of the patients had previously consumed NSAIDs, but at the entry of the study, no patient was receiving NSAID treatment, or being given injections in muscles/joints within six months before the study.

Efficacy (Subjective Data)

The parameters of pain changed during therapy in all periods. The pain scores recorded for each patient were evaluated and reproduced filling the clinical sheets previously referred, as well as described on Table 2.

Table 2 – Comparison of the efficacies of ginger and ibuprofen on muscular pain complaining patients.

Medication Efficacy	1-day trial pain relief	7-day trial pain relief	14-day trial pain relief	Adverse events
Ginger root (N=3)	-	slight/moderate	moderate	change in stool consistency
Ibuprofen (N=3)	slight/moderate	slight/moderate	total	dyspepsia nausea change in stools
Placebo (N=3)	-	-	-	dyspepsia, nausea, muscular pain change in stools

Safety

The adverse events were mainly gastrointestinal complaints (placebo period N=2, and ibuprofen period N=2), which were characterized as dyspepsia. Other complaints although with less intensity but significant were changes in stool consistency (placebo N=2, ginger extract N=1 and ibuprofen N=1) or nausea (placebo N=1 and ibuprofen N=1).

Discussion and Conclusions

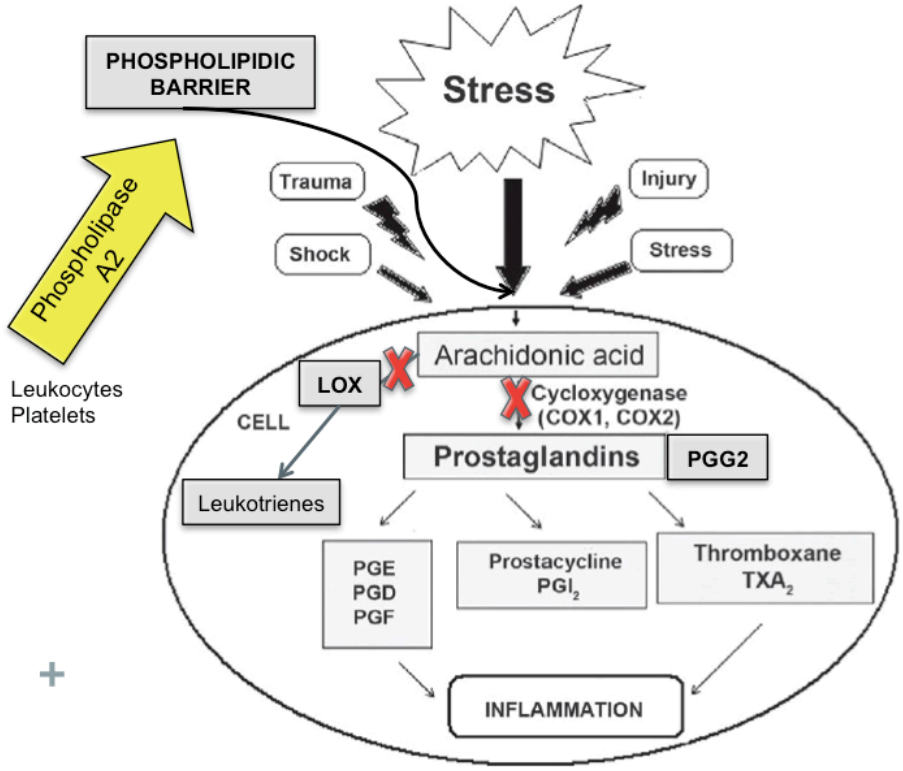
The fourteen-day consented trial demonstrated a subjective efficacy on pain level and function in patients with muscular pain of the leg, with ibuprofen being more effective than ginger root powdered extract, and also more effective than placebo, with ginger root powdered extract group exhibiting a significant subjective efficacy when compared to placebo. During the two-week treatment trial only significant gastrointestinal complaints were reported (mainly by placebo, and from the ibuprofen test-groups).

Although the use of NSAIDs in muscular pain is controversial, the fact is that many patients favour these substances for both short and long-term use. In this study, two thirds of the patients were regular NSAID users.

The subjective data obtained may imply that effectively ginger may display anti-inflammatory activity at a great level, in comparison to ibuprofen, which correlates with previous studies on its anti-inflammatory potential. Furthermore, ginger root group revealed less side effects when compared to the ibuprofen group, whose side effects reported were mainly dyspepsia, nausea and changes in stool consistency.

The hypothetic anti-inflammatory action of ginger may reside on the action of its components, mainly phenols, which are known to act on inflammatory processes. When the cellular membrane gets wounded, which is mainly composed of phospholipids, the A2 phospholipase enzyme, present in leukocytes and platelets, is activated by pro-inflammatory cytokines, as for e.g. interleukine-1 (IL-1). In turn, this enzyme leads to the degradation of the phospholipidic barrier, resulting in the production of arachidonic acid. This acid is then metabolized in chemical messengers like leukotrienes, through the action of the lipooxygenase enzyme (LO), and in prostaglandins, prostacyclins and thromboxanes through the action of the cyclooxygenase enzyme (COX) (Hilário, M. *et al*., 2006; Tjendraputra, E. *et al*., 2001; Koo, K. *et al*., 2001). The entire process can be observed on Figure 1.

Figure 1 – Scheme of the hypothetic anti-inflammatory action of ginger.



Since ginger comprises chemical substances (mainly phenols), which appear to inhibit both cyclooxygenase and lipoxygenase (dual inhibitors of COX and LOX), it can lead to a lower production of chemical messengers like leukotrienes (LTs), tumour necrosis factor (TNF) and prostaglandins (PGs), occurring systematically at the site of inflammation, helping with pain relief. Thus, this dual action might be interesting in the field of rheumatology and orthopaedics (Bliddal *et al*., 2000; Tjendraputra, E. *et al*., 2001). A recent study, conducted by Tjendraputra, E. *et al*. (2003), demonstrated that |8|-paradol, a natural constituent of ginger, was found to be the most potent COX-1 inhibitor and antiplatelet aggregation agent, whose mechanism may be related with the attenuation of the COX-1/Thromboxane synthase enzymatic activity.

The two-week period of therapy in this study might not have been sufficient for all effects of ginger root powdered extract to be discovered, and only one dose of ginger extract was applied. Future studies might look into dose-response and duration of therapy of ginger root powdered extract, if possible employing a higher dose of ginger extract. Further research on this topic could evaluate the real effect of supplementation of 1 g/daily of ginger root capsules on lipid profile, coagulation factors, other inflammatory mediators, and neuronal sensitization. Future research can also consider the effect of 1 g/daily ginger capsule on oxidative stress-related parameters, and determine whether ginger root extract can be recommended for cancer.

Chapter III - *Zingiber officinalis* botanical and phytochemical composition

Native to tropical Asia, especially between India and China, Ginger is a well-known spice composed of a knotted, thick, beige underground stem, a rhizome (Figure 2). The stem sticks up about 0,6-1,2 meters above ground with long, narrow, ribbed green leaves, and white or yellowish-green flowers, growing well in drained argillaceous areas (Proença da Cunha, A., 2006; Hasan, H. *et al*., 2012, Ali, B. *et al*., 2008, Ojewole, J., 2006).

Figure 2 - *Zingiber officinalis* botanical illustration by Francisco Manoel Blanco (Spanish botanist).

Figure 2

Table 3 - Oleoresin relative chemical composition profile of ginger dried rhizome, obtained from High Performance Liquid Chromatography (HPLC) (Hasan, H. *et al.,* 2012).

Identified components	% peak area in methanol
|6|-gingerol	25%
zingiberene	9%
β-bisabolene	4%
α-farnesene	11%
|6|-shogaol	18%
β-sesquiphellandrene	9%
α-curcumene	14%

Table 3

The constituents of ginger are numerous, and may vary, depending on the place of origin, climate and harvest, specie of ginger, maturity of the rhizome, as well as depending whether the rhizomes are fresh or dry and preparation method of the extract (Ali, B. *et al.*, 2008; Bartels, E. *et al.,* 2015).

Chemically speaking, ginger is absolutely packed with active ingredients as can be seen in Table 3. The *Materia Medica* reports that it includes a essential volatile oil (1-3%),

responsible for its characteristic odor, full of sesquiterpenoids (such as zingiberene, α-curcumene, β-bisabolene, α-farnesene) and monoterpenoids (such as β-sesquiphellandrene and camphene), major pungent phenolic principles of the lipophilic rhizome extract (gingerols and shogaols, 5-8%), lecithin, proteins, starch (60%), vitamins, minerals, and more (Proença da Cunha, A., 2006; Hasan, *et al*., 2012, Ali, B. *et al*., 2008; Young, H.-Y. *et al*., 2006).

Steam distillation of powdered ginger produces ginger oil, which contains a high proportion of sesquiterpenoid hydrocarbons. The pungency of fresh ginger is due primarily to the gingerols, which are a homologous series of phenols, and the most abundant compound is |6|-gingerol, which appears to be responsible for its characteristic taste, and is commonly used as a marker substance of ginger (Alternative Medicine Review, 2003, Young, Y. *et al*. 2005; Ali, B. *et al*., 2008; Young, H.-Y. *et al*., 2006). In another hand, the pungency of dry ginger mainly results from shogaols (mainly |6|-shogaol), which are dehydrated forms of gingerols (Ali, B. *et al*., 2008).

Chapter IV – Principal pharmacological properties of ginger, mechanisms of action and clinical indications

Nowadays, health care professionals may recommend ginger to help prevent or treat several conditions. Ginger has been widely used in Ayurvedic and Chinese medicine to treat pathologies like stomach upset, diarrhoea, digestion problems, asthma, diabetes, nausea, stroke, rheumatism, osteoarthritis and toothache described in Table 4 (Black & O'Connor, 2008; Morelli, V. *et al.*, 2003, Ehrlich, S., 2015; Ali, B. *et al*., 2008).

Table 4 – Summarized characteristics of eligible trials on ginger's potentialities.

Affections	Effects of ginger	Literature
Motion sickness, nausea and chemotherapy-induced nausea	Ginger is as effective as many traditional antiemetic pharmaceuticals	Schmid, R., *et al*., (1994) Lien, H. *et al.,* (2003) Ehrlich, S., (2015)
Digestion and functional dyspepsia	Acetone extract of ginger and its constituents enhanced the gastric emptying of charcoal meal in mice	Hu, M. *et al.* (2011) Yamahara, J. *et al*., (1990)
Blood Pressure and Asthma	Promotes smooth muscle relaxation and more elastic blood vessels	Ghayur, M. & Gilani, A. (2005) Townsend, E. *et al*., (2014)
Cholesterol and Diabetes	Lowers LDL cholesterol and triglycerides while raising HDL (↑ cholesterol excretion)	Fuhrman, B. *et al.,* (2000) Kadnur, S. & Goyal, R. (2005)
Antimicrobial activity	Effective against bacteria (Gram-positive), *H. pylori*, and fungi (*Candida albicans*)	Hasan, H. *et al*., (2012) Deba, F. *et al*., 2008)
Antiplatelet aggregation	Ginger extract inhibits platelet aggregation and thromboxane-B_2 (TXB_2) production *in vitro*	Thomson, *et al*. (2002)
Osteoarthritis	Improvement of individuals with osteoarthritis of the hip and knee	Bliddal, H. *et al.* (2000)

All mechanisms underlying ginger's principle therapeutic indications are not clearly understood, but the compounds |6|-gingerol and |6|-shogaol have been shown to have a number of interesting pharmacological activities, including antipyretic, analgesic, antitussive and hypotensive effects (Alternative Medicine Review, 2003, Young, Y. *et al*., 2005; Ali, B. *et al*., 2008).

✓ **Motion sickness, nausea and chemotherapy-induced nausea**

Ginger has long been used as a remedy to decrease nausea and vomiting associated with several conditions, however its mechanism of action is still unknown, but hypothesized that it ameliorates the nausea associated with motion sickness by preventing the development of gastric dysrhythmias and the elevation of plasma vasopressin (Lien, H. *et al*., 2003). Furthermore, recent evidences refer that ginger's anti-emetic effect may be linked to its anti-serotonin effects on both the CNS and gastrointestinal systems (Pongrojpaw, D. *et al.* 2007).

Several studies suggest that ginger may work better than placebo in reducing some symptoms of motion sickness. In one trial, of 80 new sailors who were prone to motion sickness, those who took powdered ginger had less vomiting and cold sweats compared to those who took placebo (Ehrlich, S., 2015). According to nausea, human studies suggest that 1g daily of ginger may reduce nausea and vomiting in pregnant women when used for short periods (no longer than 4 days), and found that ginger is better than placebo in relieving morning sickness and has no adverse effect on pregnancy outcome (Ehrlich, S., 2015; Vutyavanich, T. *et al*., 2001; Pongrojpaw, D. *et al.* 2007; Willetts, K. *et al*., 2003). Furthermore, a few studies suggest that ginger may reduce the severity and duration of nausea and vomiting, during chemotherapy (Zick, S. *et al*., 2009). Pillai, A. *et al.* (2011) concluded that ginger root powder was effective in reducing the severity of acute and delayed chemotherapy-induced nausea and vomiting, as additional therapy to Ondansetron and Dexamethasone (standard antiemetics used in the study) in patients receiving high emetogenic chemotherapy.

In another trial, 13 volunteers with a history of motion sickness underwent circular vection, during which nausea (scored 0-3, i.e., none to severe), electrogastrographic recordings, and plasma vasopressin levels were assessed with or without ginger pre-treatment in a crossover-design, double-blind, randomized placebo-controlled study. Pre-treatment with ginger (1,000 and 2,000 mg) reduced the nausea, tachygastria, and plasma vasopressin. Ginger also prolonged the latency before nausea onset and shortened the recovery time after vection cessation, which implies that ginger may act as a novel agent in the prevention and treatment of motion sickness (Lien, H. *et al*., 2003).

Other double-blind studies have been performed, and demonstrate a positive effect of ginger on motion sickness, shown to be as effective as many traditional antiemetic pharmaceuticals for seasickness such as domperidone, dimenhydrinate, scopolamine, cinnarizine, cyclizine and meclozine (Schmid, R. *et al*., 1994).

Schmid, R. *et al*., (1994) performed a study on a total of 1475 tourist volunteers who were joining a whale safari in Norway, in order to evaluate and compare the efficacy and tolerability of 7 commonly used drugs for the prevention of seasickness - cinnarizine, cinnarizine + domperidone, cyclizine, dimenhydrinate + caffeine, ginger root, meclozine + caffeine and scopolamine. The passengers were asked to take the study medications about 2 hours prior to departure of the boat, done under supervision, and to return completed questionnaires.

Table 5 – Drug efficacy (Schimd, R. *et al.,* 1994).

	Seasickness (%)			
Drugs	None	Slight/Moderate	Severe/Vomiting	Vomiting
Cinnarizine	80.3	10.1	9.6	7.6
Cinnarizine/Domperidone	77.7	16.6	5.7	4.8
Cyclizine	80.7	9.1	10.2	6.3
Dimenhydrinate/Caffeine	81.4	10.8	7.8	4.1
Ginger root	78.3	12.3	9.4	7.9
Meclozine/caffeine	79.1	13.1	7.8	5.2
Scopolamine	75.2	11.5	13.3	10.2

Table 5 shows that in the various treatment groups, 9.1%-16.6% revealed at least slight seasickness, with the rates for vomiting varying from 4.1%-10.2%. Furthermore, those using scopolamine had tendency to more illness in comparison to the other treatment groups, and also reported visual problems slightly more frequent than with other medications. None of the various studied medications offered complete protection against seasickness, only scopolamine showing less efficacy (Schmid, R. *et al*., 1994). Ginger was shown to be an agent almost as potent as the others tested, and particularly fascinating, as it is said not to act on the Central Nervous System, but on the Gastric System (Holtmann, S. *et al*., 1989).

✓ **Digestion and functional dyspepsia**

Ginger root powder has long been used in traditional medicine for alleviating the symptoms of Gastro Intestinal (GI) illnesses. In this context, Yamahara, J. *et al*., (1990) found that the acetone extract of ginger and its constituents enhanced the gastric emptying of charcoal meal in mice.

Recently, Hu, M. *et al.* (2011) focused on the evaluation of ginger effects on gastric motility and emptying, abdominal symptoms and hormones that influence motility in dyspepsia. Eleven patients with functional dyspepsia were studied twice in a randomized double-blind

manner (after an 8-hour fast, they ingested 3 ginger capsules (1.2g in total) or placebo, followed after 1 hour by 500 ml low-nutrient soup.

Figures 3 and 4 – Fig. 3 – Gastric emptying after ginger and placebo intake in patients with functional dyspepsia who consumed 500 ml of low-nutrient soup; Fig. 4 – Frequency of antral contractions after ginger and placebo in patients with functional dyspepsia (Hu, M. *et al.,* 2011).

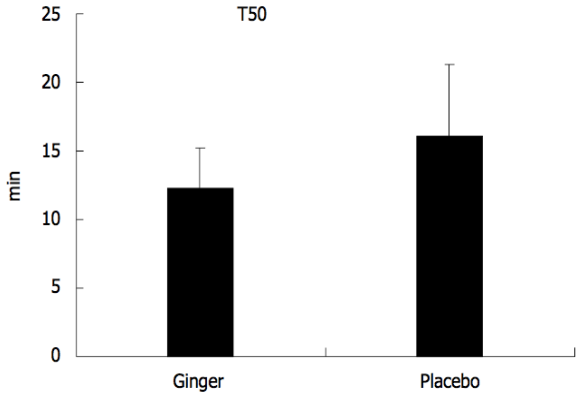


Fig.3

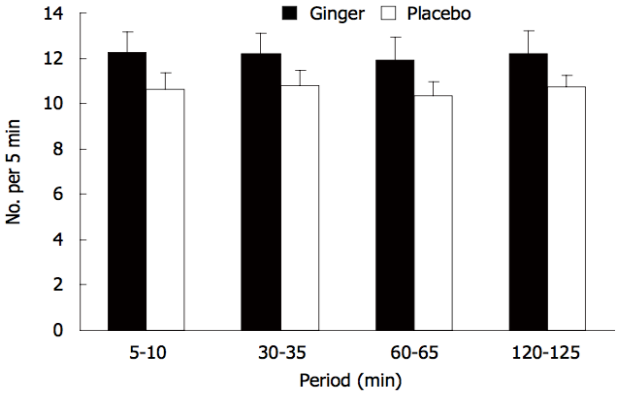


Fig.4

As can be seen on Figure 3, gastric emptying was more rapid after ginger intake than with placebo |median (range) half-emptying time (T50: 12.3 (8.5-17.0 minutes)| vs. 16.1 (8.3-22.6 minutes), and there was a trend for smaller antral area after ginger. Figure 4 demonstrates that there was a trend for a higher frequency of antral contractions after ginger intake. In summary, it was confirmed that the acceleration of gastric emptying by ginger was possible in patients with functional dyspepsia, although further studies on specific groups (as for example performed in patients with known delayed gastric emptying), are required in order to determine whether ginger can be a useful therapeutic approach.

✓ Blood Pressure and Asthma

Many studies, mainly performed with rats, have suggested that ginger extracts exert many direct and indirect effects on blood pressure and heart rate, as the use of ginger in cardiovascular diseases has long been known (Chen, Z. *et al*., 2009).

Lately, Ghayur, M. & Gilani, A. (2005) performed a study to investigate the blood pressure (BP) lowering potential of the crude extract of fresh ginger in anesthetized rats, the effect of ginger extract on guinea pig atria and the effect of the extract on the rabbit aorta in comparison to a commonly prescribed antihypertensive (verapamil), as well as the possible mechanism of action was explored using isolated cardiovascular preparations.

Figures 5 and 6 – Fig. 5 - Typical tracing of showing the hypotensive effect of ginger crude extract (Zo.Cr) in comparison to norepinephrine (NE) and acetylcholine (ACh) on blood pressure (BP) in anesthetized rats; Fig. 6 – Typical tracing showing the cardiodepressant effect of the ginger crude extract (Zo.Cr) in comparison to verapamil in isolated guinea pig atrium (Ghayur, M. & Gilani, A. (2005).

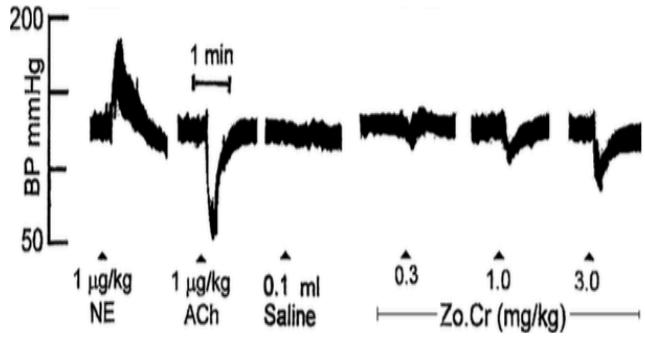


Fig. 5

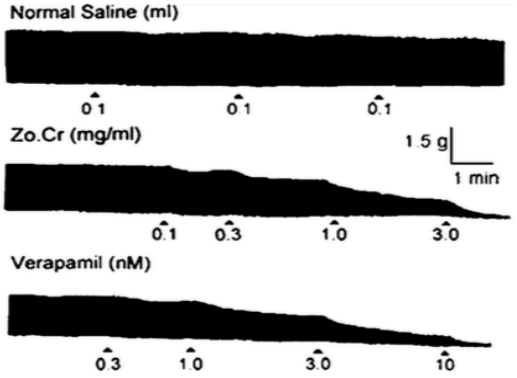


Fig. 6

The aqueous-methanolic extract of fresh ginger induced a dose-dependent (0.3-3.0 mg/kg) fall in blood pressure of rats under anesthesia (Figure 5). On the other hand, in the guinea pig paired atria, the extract caused an inhibitory effect on the spontaneous force and beating rate of atrial contractions (Figure 6). This fact may be correlated with the possible mechanism of action by which ginger may act, as in the isolated guinea pig paired atria the extract decreased the force and rate of spontaneous atrial contractions in a dose-dependent manner, similar to verapamil, known as a standard calcium antagonist (Chen, Z., *et al*., 2009).

Regarding the rabbit aorta, routinely used for the screening of antihypertensive Calcium Channel Blockers (CCBs), the CCB effect mediated by the crude extract in the vascular tissues was found to be more potent than the effect exhibited in cardiac tissue. In addition, the fresh ginger extract relaxed the phenylephrine-induced vascular contraction at a dose 10 times higher than that required against K^+-induced contraction. Also, CCB activity was confirmed when the crude extract shifted the calcium-dose-response curves to the right similar to the effect of verapamil. In conclusion, these data indicate that the arterial blood pressure-lowering effect of ginger is mediated through the blockade of voltage-dependent calcium channels and effective, and that ginger may act as a potent vasodilator.

Natural herbal remedies, including ginger, have long been used, as well, to treat respiratory conditions. Many individuals suffering from asthma (exaggerated airway narrowing and increased airway inflammation) search for herbal therapies in order to self-treat their asthma symptoms, however little is known concerning how these compounds work in the airways

(Townsend, E. *et al*., 2014). With this in mind, Townsend, E. *et al*., (2014) conducted a study in order to determine whether ginger extract compounds (|6|-gingerol, |8|-gingerol or |6|-shogaol) potentiate β-agonist-induced airway smooth muscle (ASM) relaxation, (as β-agonists represent the first-line therapy to alleviate asthma symptoms by acutely relaxing the airways), and if so, define the mechanism(s) of action responsible for this potentiation.

For the study, the researchers used human ASM that contracted in organ baths, and guinea pig tracheal rings. The tissues were relaxed dose-dependently with a β-agonist (isoproterenol) in the presence of several vehicles (|6|-gingerol, |8|-gingerol or |6|-shogaol 100 μM), and whose relaxation results can be seen on Table 6. Cellular experiments used primary human ASM cells, and purified phosphodiesterase (PDE) 4 or phospholipase C-β enzyme was used to assess the inhibitory activity of ginger components using fluorescent assays.

Table 6 – Summary of the effects of ginger components on isoproterenol half-maximal effective concentration ASM relaxation contracted by acetylcholine (Townsend, E. *et al*., 2014).

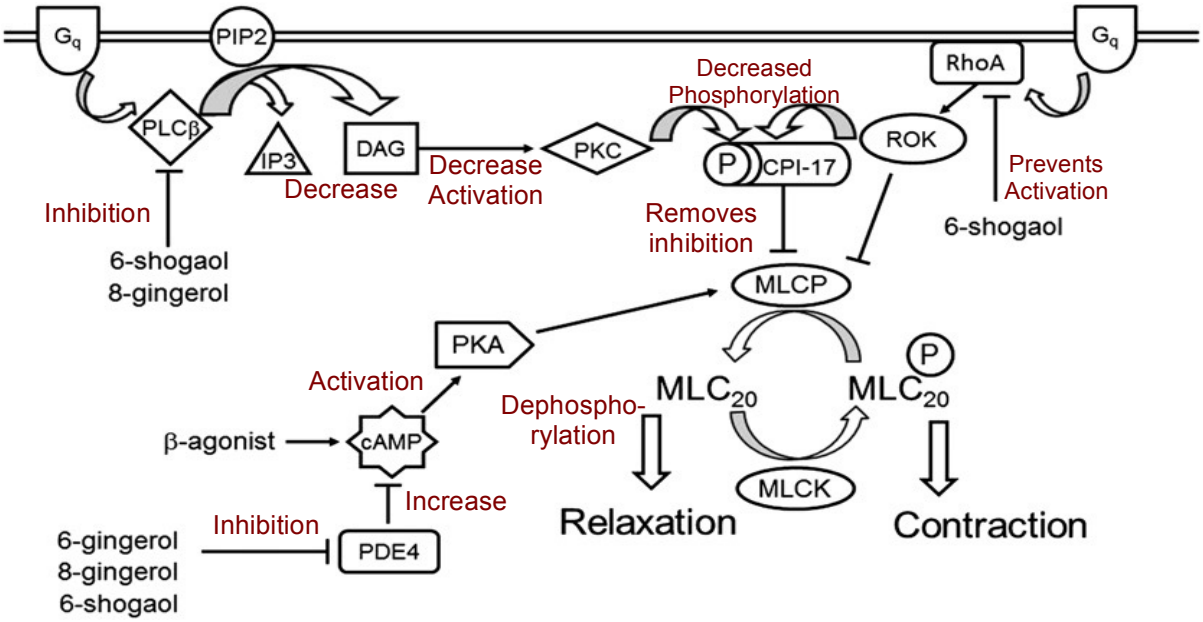
	Isoproterenol EC_{50} (nM)	
	Human ASM	**Guinea Pig ASM**
Vehicle (0.2% DMSO)	28.5±2.6	8.9±1.9
|6|-gingerol (100 μM)	1.7±0.6	1.5±0.3
|8|-gingerol (100 μM)	2.1±0.5	1.2±0.2
|6|-shogaol (100 μM)	1.1±0.5	0.8±0.1
|10|-gingerol (100 μM)	-	5.8±2.1
U-73122 (5 μM)	-	3.2±1.0

Definition of abbreviations: ASM – airway smooth muscle, DMSO – dimethyl sulfoxide, EC_{50} – half-maximal effective concentration.

Table 6 lists the results for human and guinea pig isoproterenol-induced relaxation. In human ASM tissue contracted with acetylcholine (ACh), 100 μM of |6|-gingerol, |8|-gingerol or |6|-shogaol revealed minimal relaxation when compared with vehicle controls (0.2% DMSO). As all tissues received either a single treatment of vehicle (0.2% DMSO) or 100 μM of |6|-gingerol, |8|-gingerol or |6|-shogaol concurrently with the 300-pM isoproterenol dose, one can say that, in comparison to the vehicle, all active components of ginger significantly potentiated the isoproterenol-induced relaxation oh human ASM. Furthermore, it was observed that |6|-shogaol was the greatest potentiator of relaxation. Similar results were verified in guinea pig ASM tissues contracted with ACh and subjected to identical treatments.

The mechanisms of action, underlying the action of the tested ginger components, can be seen on Figure 7. In summary, |6|-gingerol, |8|-gingerol, and |6|-shogaol potentiate β-agonist-induced relaxation of the airway smooth muscle by inhibiting both phosphodiesterase 4D (PDE4) and phosphatidylinositol-specific phospholipase C isoform β (PLC β), leading to the downstream regulation of contractile proteins, which suggest that natural compounds can work in combination with traditional asthma prescriptions in order to relieve its symptoms and exacerbations.

Figure 7 – Mechanisms of action of the isolated components of ginger, |6|-gingerol, |8|-gingerol and |6|-shogaol, with multiple intracellular targets that potentiate β-agonist–induced relaxation in ASM (adapted from Townsend, E. *et al*., 2014).



Definition of abbreviations: DAG – Diacylglycerol, G_q – G protein-coupled receptor type q, PIP2 – Phosphatidylinositol-4,5-bisphosphate, PLC β – phospholipase C isoform β, MLC_{20} – myosin light chain 20, MLCK – MLC kinase, MLCP – MLC phosphatase, cAMP – 3'-,5'-cyclic adenosine monophosphate, PKA – protein kinase A, IP3 – inositol triphosphate, PKC – protein kinase C, CPI-17 – 17 kD protein kinase C-potentiated inhibitory protein of type 1 protein phosphatase, RhoA – Ros homolog gene family member A, ROK – Ros homolog gene family kinase (Townsend, E. *et al*., 2014).

✓ **Cholesterol and Diabetes**

Coronary artery disease may develop as a result of various risk factors, including increased plasma Low Density Lipoprotein (LDL) levels, commonly known as "bad cholesterol", as well as LDL modifications, such as oxidation or aggregation. The consumption of nutrients rich in phenolic antioxidants have been shown to attenuate the development of atherosclerosis (Fuhrman, B. *et al.*, 2000, Ojewole, J., 2006).

A study conducted with apolipoprotein E-deficient mice, which develop atherosclerotic plaques which resemble the lesions found in humans, revealed a significant reduction (76%) in cellular cholesterol biosynthesis rate in peritoneal macrophages derived from the mice that consumed a 250 µg/day of ginger extract for 10 weeks compared to those from controls, both *in vivo* and *in vitro*, revealing a reduction on the levels of triglycerides in plasma and LDL by 27% and 58%, respectively. Additionally, this study confirmed that ginger extract, whose mainly antioxidative active principles were gingerols and shogaols, as well as some related phenolic ketone derivatives, had exhibited a direct antioxidative effect against LDL oxidation (Fuhrman *et al.*, 2000). Human trials are required, as this potent ginger activity is still humanly unexplored.

As hyperlipidemia is generally associated with elevated levels of blood glucose and insulin levels (diabetes), Kadnur, S. & Goyal, R. (2005) undertook a study in order to explore the possible beneficial effects of ginger in fructose-induced hyperlipidemia, hyperinsulinemia and hyperglycemia in four groups of rats. Each group of animals was administered vehicle or drugs daily for 3 weeks, and a normal diet:

Group I – normal diet + water *ad libitum* + vehicle solvent;

Group II – normal diet + water with 10% fructose + vehicle solvent (control)

Group III – normal diet + water with 10% fructose + methanolic extract of ginger (250mg/kg)

Group IV – normal diet + water with 10% fructose + ethyl acetate extract of ginger (250mg/kg)

Table 7 – Evaluation of ginger extracts on various parameters in fructose-induced hyperlipidemia in rats (values are mean ± SE of 6 rats in each group) (Kadnur, S. & Goyal, R., 2005).

	Groups Tested			
Serum Parameters	**Normal Control**	**Hyperlipidemia Control**	**Methanolic ginger extract**	**Ethyl acetate ginger extract**
Glucose (mg/dl)	86.5±1.9	116.1±3.4	95.1±1.7	114.1±2.5
Insulin (µU/ml)	23.6±1.2	41.3±0.9	34.0±1.1	41.0±0.6
Cholesterol (mg/dl)	73.0±1.2	106.1±1.4	84.2±1.5	92.7±1.0
Triglycerides (mg/dl)	69.7±1.2	152.0±3.9	88.2±2.8	111.1±2.3
HDL cholesterol (mg/dl)	17.5±0.6	19.3±0.5	17.4±0.4	17.6±0.4
LDL-cholesterol (mg/dl)	41.5±1.4	56.3±1.3	49.0±1.9	52.9±0.6
VLDL-cholesterol (mg/dl)	13.9±0.2	30.3±0.7	17.6±0.5	22.2±0.4
Body weight (g/rat)	243.3±3.3	378.3±3.0	326.7±2.1	335.0±2.2

The results of the study, summarized in Table 7, demonstrate that the treatment with an extract of *Zingiber officinalis* is effective in reducing both elevated lipid profile and elevated glucose levels, having the methanolic extract of ginger clearly demonstrated a better response as it also prevented partially but significantly the elevated insulin levels in fructose-

fed rats. Additionally, the results show significant reduction in body weight on treatment with both extracts of ginger, which suggest that ginger may be useful in conditions of *Syndrome-X* (*Metabolic Syndrome*) and associated disorders, as it can reduce the elevated hypertriglyceride, VLDL-cholesterol levels and hyperinsulinemia (Gonlachanvit, S. *et al.,* 2003). Recently, Ojewole, J. (2006) performed a study on diabetic rats, and compared the action of chlorpropamide (reference hypoglycemic agent used in the study) with the ethanolic extract of *Z. officinalis* dried rhizomes, and found that both produced significant reductions in the blood glucose levels of fasted normal and fasted streptozotocin-induced diabetes mellitus rats.

✓ **Antimicrobial activity**

The antimicrobial activity against both bacteria and fungi by *Zingiber officinalis* has been described by several studies, which attribute this double-action to the presence of isolated phenolic compounds in ginger's root, both gingerol and shogaol, lipid-soluble phenolic compounds (Hasan, H. *et al*., 2012, Park, M. *et al.,* 2008).

Bajpai, V. *et al*., (2009) as well as other researchers, are in agreement with the previous statement, and refer that it seems reasonable to assume that the antimicrobial mode of action might be related to the phenolic compounds present in ginger, as most of the studies conducted on their mechanism of action have focused on their effects on cellular membranes (Bajpai, V. *et al*., 2009; Hasan, H. *et al*., 2012). Furthermore, they refer that phenolic compounds attack cell walls and cell membranes (affecting their permeability and release of intracellular constituents like ribose, for instance), and also interfere with membrane functions (electron transport, nutrient uptake, protein, nucleic acid synthesis and enzyme activity), highlighting that these phenolic compounds might have several invasive targets which can lead to the inhibition of microbial pathogens (Bajpai, V. *et al*., 2009).

Table 8 – Antimicrobial activities of the methanolic extract of *Zingiber officinalis* rhizome and methanol (negative control) (Hasan, H. *et al*., 2012).

	Inhibition zone diameter (mm) at different concentrations of the MeOH extract (mg/dl)				
Tested Microorganisms	**50**	**25**	**12.5**	**6.25**	**3.1**
Gram-positive					
Staphylococcus epidermidis	16.5	12	-	-	-
Staphylococcus aureus	17	16	14	-	-
Gram-negative					
Proteus sp.	12.5	-	-	-	-
Klebsiella sp.	14	10	-	-	-

Escherichia coli	12	-	-	-	-
Enterococcus sp.	14.5	12	-	-	-
Pseudomonas florescent	10	-	-	-	-
Fungi					
Candida albicans	13.5	-	-	-	
Methanol (negative control)	-	-	-	-	

Table 8 results on antimicrobial activities of the extract of *Zingiber officinalis* clearly show that this extract is more effective against Gram-positive bacteria when compared to the Gram-negative ones *in vitro*, assessed by the presence or absence of inhibition zones, whose higher resistance can be explained by the complexity of the Gram-negative bacteria cell wall, whose external membrane yields highly hydrophilic surfaces whereas the negative charge present on the surface of the Gram-positive bacteria wall may reduce their resistance to antibacterial compounds (Hasan, H. *et al*., 2012; Michielin *et al*., 2009).

The results on the antifungal activity assay showed that the extract of ginger also displays inhibitory effects on the growth of *Candida albicans*, which may be a result of the action of the monoterpenes present in the extract, reported to have a wide range of antifungal activity, through the disruption of the fungal membrane integrity (Hasan, H. *et al*., 2012; Deba, F. *et al*., 2008).

Recently, Mahady, G. *et al*., (2003) tested the *in vitro* effects of ginger on 19 strains of *Helicobacter pylori* (primary etiological agent associated with dyspepsia, peptic ulcer disease and development of gastric and colon cancers), including 5 $CagA^+$ strains, and the obtained results are listed in Table 9.

Table 9 – Minimum inhibitory concentrations of ginger extracts and gingerols in 5 $CagA^+$ strains of *H. pylori* (Mahady, G. *et al.,* 2003).

	Minimum inhibitory concentrations and 5 $CagA^+$ strains of *H. pylori*				
HP Strain 43504	**M23-3**	**GTD7-13**	**G1-1**	**SS1**	**ATCC**
Ginger root-MeOH	6.25	25.0	6.25	6.25	25.0
Methanol-F2	0.78	6.25	1.56	0.78	6.25
|6|-gingerol	6.25	12.0	12.5	3.125	6.25
|8|-gingerol	3.125	6.25	6.25	3.125	6.25
|10|-gingerol	1.56	6.25	1.56	1.56	6.25
|6|-shogaol	12.5	25.0	12.5	12.5	25.0

*$CagA^+$ is the strain-specific *H. pylori* gene that has been linked to the development of premalignant and malignant histological lesions, and infections caused by $CagA^+$ strains significantly increase the risk of developing severe gastric inflammation, atrophic gastritis and noncardia gastric adenocarcinoma (Mahady, G. *et al*., 2003).

The researchers indicated that the methanolic extract of ginger rhizome inhibited the growth of all 19 strains of *H. pylori in vitro*, with a minimum inhibitory concentration (MIC) range of 6.25 to 50 µg/ml. Furthermore, one fraction of the crude extract, containing the gingerols, was active and inhibited the growth of all *H. pylori* strains with a MIC range of 0.78 to 12.5 µg/ml, with significant activity against the $CagA^+$ strains, results that may contribute to support the chemopreventive effects of ginger.

Recently, Zick, S. *et al.* (2011) evaluated the effects of ginger in colon mucosa in people at normal risk for colorectal cancer, and found that ginger appears to potentially decrease eicosanoid levels (inflammatory products), through the inhibition of their synthesis from the arachidonic acid, and thus reduce inflammation, but warrant further study due to small sample size.

Park, M. *et al.* (2008) also found that |10|-gingerol present in ginger's rhizome evidenced potent antibacterial activities *in vitro* against anaerobic bacteria associated with periodontitis of the human oral cavity by activity-guided assays.

✓ **Antiplatelet aggregation**

Ginger has shown to exhibit antithrombotic activity, as its extract was found to inhibit platelet aggregation and thromboxane-B_2 (TXB_2) production *in vitro* (Srivastava, K. & Mustafa, T., 1989; Nicoll, R. & Henein, M., 2007).

Recently, Thomson, M. *et al*., (2002) investigated the *ex vivo* effect of an aqueous extract of raw ginger on the synthesis of thromboxane-B_2 (TXB_2), prostaglandin-E_2 (PGE_2), cholesterol and triglyceride levels in the serum of normal rats, using two routes of administration – oral and intraperitoneal (IP), as well as two doses (50 mg/kg and 500 mg/kg) in a four-week trial.

Figures 8 and 9 – Fig. 8 – Effect of aqueous extracts of ginger on the serum levels of PGE_2 in rats. *significantly different from control (normal saline) using Student's *t*-test. Fig. 9 – Effect of aqueous extracts of ginger on the serum levels of TXB_2 in rats. *significantly different from control (normal saline) using Student's *t*-test (Thomson, M. *et al*., 2002).

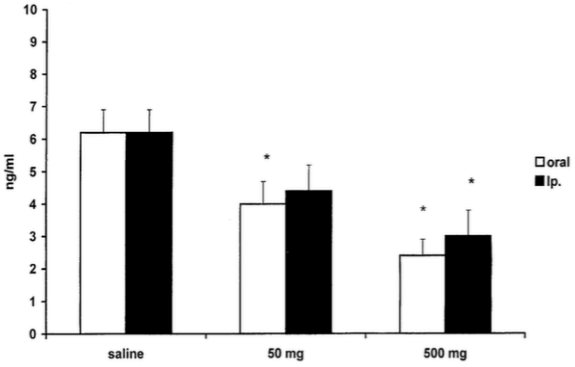


Fig. 8

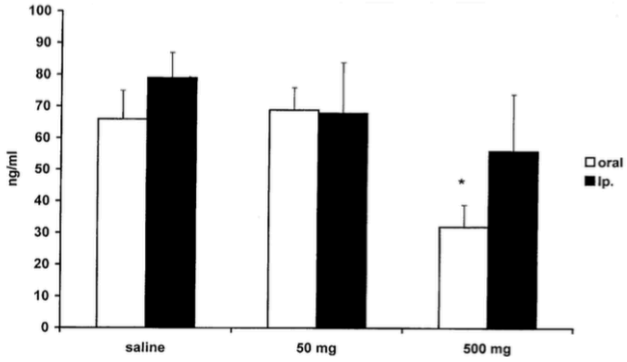


Fig. 9

Figures 8 and 9 show the effects of the administration of the aqueous extract of ginger on the synthesis of PGE_2 and TXB_2. The oral administration of ginger, at low doses (50mg/kg), significantly reduced the levels of serum PGE_2. However, high oral dose intake of ginger (500 mg/kg) was more effective in reducing the synthesis of PGE_2. Additionally, PGE_2 levels were significantly lower than the saline control in rats given 500mg/kg ginger extract either orally or IP. It can also be seen that the higher oral dose of ginger (500mg/kg) had significantly reduced TXB_2 levels in the serum, rather than the lower dose. To summarize, the unique ability of ginger to inhibit the synthesis of both PGE_2 and TXB_2 is clinically important, because its daily intake for a prolonged period will neither lead to side-effects or complications as normally occurs with non-steroidal anti-inflammatory drugs (NSAIDs).

- ✓ **Osteoarthritis**

Traditional medicine has used ginger for centuries to reduce inflammation, and there is some evidence that ginger may help reduce pain from osteoarthritis (OA). Preclinical research has shown that both gingerols and shogaols present in ginger extract act as cyclooxygenase inhibitors of (COX), particularly the inducible form of COX (COX-2), rather than the constitutive form (COX-1), as well as leukotriene synthesis (explained by the action of ginger inhibiting lipooxygenase) and production of pro-inflammatory cytokines *in vitro* (Bartels, E. *et al*., 2015), Black & O'Connor, 2008; Morelli, V. *et al.*, 2003; Chrubasik, J. *et al.*, 2007). In addition, Black & O'Connor (2008) found that 6-gingerol and ginger extracts acutely reduce paw edema and pain behaviors in rodents within 30 minutes.

Ginger and/or its constituents are thought to act both peripherally, by inhibiting the release of prostaglandins (PGs) and leukotrienes (LKs), and centrally, potentially by interacting with a vanilloid receptor, which is known to play a role in processing nociceptive signals (Black & O'Connor, 2008; Cortright, Krause, & Broom, 2007; Gregory, P. *et al*., 2008).

Bartels, E. *et al.,* (2015) conducted a study with the aim of assessing the clinical efficacy and safety of oral ginger for symptomatic treatment of osteoarthritis (OA), whose inclusion criteria were randomized controlled trials comparing oral ginger treatment with placebo in OA patients aged above 18, and the outcomes were measured by the reduction in pain and reduction in disability. The authors found that after ginger intake, a statistically relevant pain reduction SMD = -0.30 (95% CI), as well a statistically significant reduction in disability SMD = -0.22 (95% CI) were seen both in favour of ginger. Ginger was modestly efficient and reasonably safe for treatment of osteoarthritis.

Recently, Naderi, Z. *et al.,* (2015) conducted a study whose aim of investigation was to examine the effect of ginger powder supplementation on some inflammatory markers in patients suffering from knee osteoarthritis, in a double-blind randomized placebo-controlled clinical trial with a follow-up period of 3 months conducted on 100 outpatients with moderately painful knee osteoarthritis. Patients were randomly divided into two groups: ginger group (GG) and placebo group (PG), and both groups received two identical capsules on a daily basis for 3 months. Each ginger capsule contained 500 mg of ginger powder, whereas the placebo contained 500 mg of starch, with serum samples being collected prior and after the intervention, which can be observed in Table 10. Serum concentration of nitric oxide (NO) and hs-C-reactive protein (hs-CRP) were measured using enzyme-linked immunosorbent assay kits, and no significant differences between both groups in terms of inflammatory markers (i.e. NO and hs-CRP) were found prior to the trial.

Table 10 - Comparison of mean of NO and CRP concentration in both ginger and placebo groups prior to and after intervention (Naderi, Z. *et al.,* 2015).

Variables	Ginger group	Placebo group	p^a
Energy (kcal/dl)			
Prior to	1904.2±325.4	1859.7±272.2	0.6
After	2010.4±401.0	1997.4±213.1	0.3
Cholesterol (mg/dl)			
Prior to	302.02±102.82	310.21±123.02	0.08
After	295.02±87.82	301.02±95.12	0.6
NO (µmol/L)			
Prior to	29.02±0.82	29.21±1.02	0.53
After	26.02±1.82	27.02±0.32	<0.001
Change	-3.0±0.72	-2.01±0.19	<0.001
CRP (mg/L)			
Prior to	11.06±1.43	11.21±1.20	0.56
After	8.47±1.62	9.66±1.31	<0.001
Change	-2.58±1.47	-1.54±1.12	<0.001

Definition of abbreviations: CRP – C-Reactive Protein, NO – Nitric Oxide, p^a – Student *t* test.

Table 10 presents the effect of ginger and placebo (starch) on CRP and NO of the patients at the beginning of the study and 3 months after the study. As can be seen, there was no significant difference between the two groups in CRP and NO concentrations prior to the intervention. However, after supplementation with ginger, a significant decrease was observed in serum concentration of CRP and NO in the GG, but not in the other group. At the end of the study, both CRP and NO concentrations decreased more in the experimental group rather the control group. Furthermore, no statistically significant difference was found between pre- and post-intervention parameters for daily energy.

In conclusion, this study found that in patients who suffered from moderate knee OA, the serum concentration of CRP and NO 3 months after ginger supplementation was significantly different from the data obtained at the beginning of the study, and Naderi, Z. *et al.* (2015) referred that the possible mechanism by which ginger reduces inflammation in patients with OA is summarized as follows: activation of synovial cells in the joints leads to the release of two key cytokines involved in the inflammation and degradation of joints, TNF-α and IL-1β. Both mediators induce NF-kβ, which is a ubiquitous eukaryotic transcription factor with a critical role in inflammatory pathways. This nuclear factor brings about inflammation by activating iNOS, COX-2 pathway, and lipoxygenase pathway and by inducing the secretion of inflammatory cytokines. The gingerols and shogaols present in ginger are the compounds responsible for the decrease in the two pro-inflammatory factors of TNF-α and IL-1β in osteoarthritic cartilage. In synoviocytes, these compounds decrease the IL-1β- or TNF-α-induced expression of TNF-α mRNA and protein, the TNF-α-induced production of COX2, and the TNF-α-induced activation of the NF-kβ. In addition, these vital compounds suppress the synthesis of prostaglandin (PG) and leukotriene (LK) by inhibiting the COX-2 and lipoxygenase pathways and also inflammation-involved pathways, so this way, they can diminish the inflammation.

In another study conducted by Zakeri, Z. *et al.* (2011), the authors evaluated the effects of ginger extract on knee pain, stiffness and difficulty in patients with knee OA, and found that pain reduction was more significant in ginger group than placebo, and reduction in morning stiffness and difficulty were statistically greater in the ginger group, rather than the placebo group. Additionally, patients with less duration of the disease showed more improvement, which suggests that if the treatment is started at an earlier stage of the disease, before the formation of complete knee joint destruction, the results will be much better.

Due to the previously referred strong anti-inflammatory and antioxidant activities exerted from ginger, Shukla, Y. & Singh, M. (2007) reviewed several articles on its anti-carcinogenic and anti-mutagenic activities, and found that a significant number of *in vitro* and laboratory animal studies provide substantial evidences that ginger and its organic pungent vallinoid compounds (mainly |6|-gingerol and |6|-paradol, shogaols and zingerone) are effective inhibitors of the carcinogenic process, previously confirmed by Surh, Y. *et al.* (1998), and recently by Kim, M. *et al.* (2010).

Chapter V – Traditional Chinese Medicine concepts and ginger (*jiang*) applications

Traditional Chinese Medicine (TCM), originated in ancient China, has evolved over the years, and it encompasses many different practices, including acupuncture, moxibustion (burning of an herb above the skin to apply heat to acupuncture points), Chinese herbal Medicine, ***tui na*** (Chinese Therapeutic Massage), dietary therapy and mind practices, such as ***qi gong*** (prevention practice that combines specific movements/postures, coordinated breathing and mental focus). TCM practitioners mainly use these techniques to prevent and treat health problems (Greten, H., 2007; NCCAM, 2009; Hempen, C. & Chow, V., 2006).

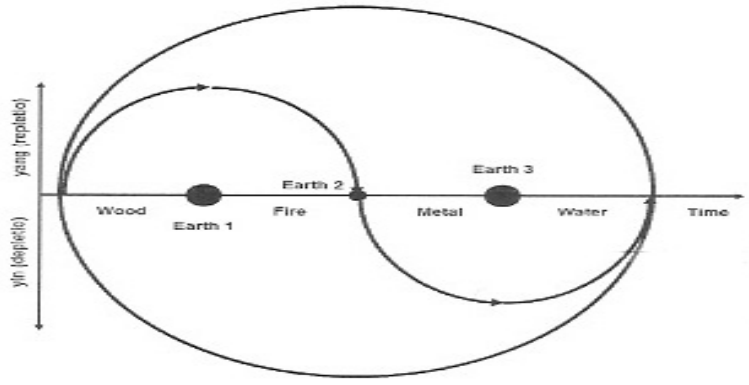
The ancient beliefs on which TCM is based include the following concepts, which are of interest in understanding the history of TCM (NCCAM, 2009; Nong, S., 2015; Greten, H. 2010; Hempen, C. & Chow, V., 2006):

- ✓ The human being is a part of an interwoven network of cosmic energies, as "man is part of the holistic entity, and should be analysed or interpreted with reference to the whole",

- ✓ Harmony between two opposing yet complementary forces, called ***Yin*** and ***Yang***, supports health, and disease results from an imbalance between these two forces. *Yin* and *Yang* can describe two relative aspects of the same phenomena, such as for example "*Yin* representing the shadier side of a slope, and *Yang* the sunnier side", or they can describe two different objects like sky and earth.

- ✓ The **Five Elements Theory** (Figure 10) — ***wood*** *(creation of potential)***,** ***fire*** *(transformation of potential into function)***,** ***earth***, ***metal*** *(relative lack of energy)***,** and ***water*** *(regeneration)* — which symbolically represent all natural phenomena, including the stages of human life, and explain the functioning of the body and how it changes during disease.

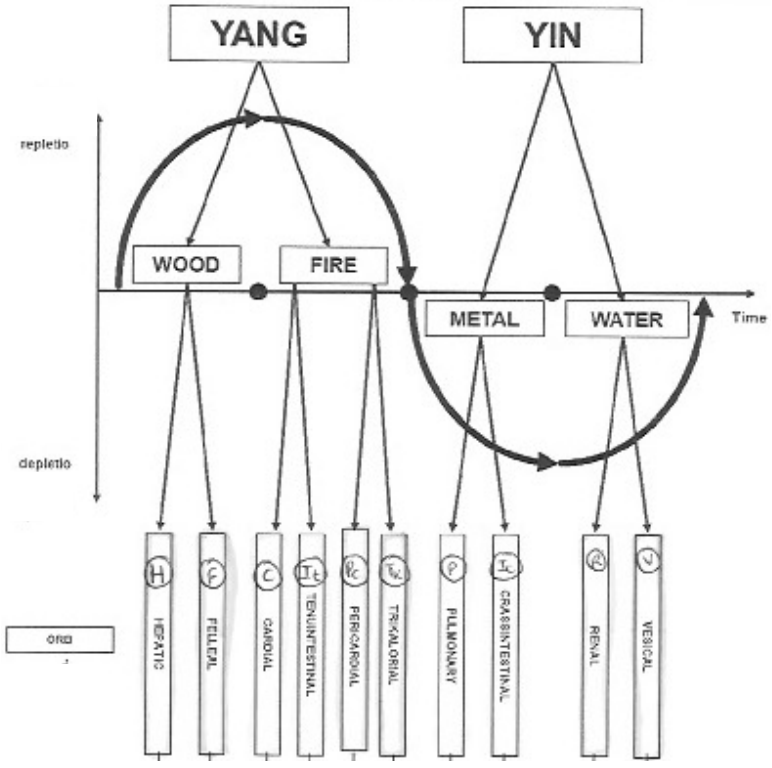
Figure 10 – The Five Element spectrum – regulative sinus curve (Greten, H., 2007).



- ✓ ***Qi***, is the vital energy constituting the human body, and performs multiple functions in maintaining its health (according to the *Heidelberg Model*, *qi* is "the vegetative capacity to function of a tissue or organ, which can cause the sensation of pressure, tearing or flow").

- ✓ The **System of the 12 Orbs (*Jing Mai*)** – TCM believes there is a distribution network for the fundamental substances of *qi*, blood and body fluids throughout the body, which links different areas of our body together, and whose pathways make up a comprehensive yet complex body map that supplies vital energy to every part of the body. The flow of *qi* in the Orbs System concentrates in certain areas of the skin's surface, small point areas known as "acupuncture points". The word "***orb***" corresponds to "a circle or group of diagnostically significant signs and findings grouped and named after organs or the region where some of the symptoms take place". The system of the main 12 Orbs, designed on Figure 11, correspond to the *Yin* (*jing*) and *Yang* (*luo*) organs plus the ***Tricaloric*** and ***Pericardium*** - *Yin* represented by the liver (***hepatic orb***), heart (***cardiac orb***), spleen (***lienal orb***), lungs (***pulmonary orb***) and kidneys (***renal orb***), and *Yang* represented by the gall bladder (***felleal orb***), small intestine (***tenuintestinal orb***), stomach (***stomachal orb***), large intestine (***crassintestinal orb***) and bladder (***vesicle orb***). Additionally, there are eight extraordinary vessels (*Qi Jing Ba Mai*), divergent channels (*Jing Bie*), sinew channels (*Jing Jin*) and network channels (*Luo Mai*).

Figure 11 – The 12 Orb System – the *Yin & Yang* arbogram for diagnosis (Greten, H., 2010).



Focusing on the Chinese Herbal Medicine, the Chinese *Materia Medica* (a pharmacological reference book used by TCM practitioners) describes thousands of medicinal substances - primarily plants, but also some minerals and animal products, in which different parts of plants, such as leaves, roots, stems, flowers, and seeds, are reported to be used. In TCM herbs are often combined in formulas and given as teas, capsules, liquid extracts, granules, or powders (NCCAM, 2009; Nong, S., 2015; Greten, H. 2010; Hempen, C. & Chow, V., 2006).

Herbal medicines used in TCM are sometimes marketed in other countries, as well as in Portugal, as dietary supplements. The Portuguese *Autoridade Nacional do Medicamento e Produtos de Saúde* (INFARMED, I. P.) regulations for dietary supplements are less stringent.

In spite of the widespread use of TCM in China and its use in the West, rigorous scientific evidence of its effectiveness is limited, and so, in other countries, people only seek TCM as a complementary health approach. TCM can be difficult for researchers to study because its treatments are often complex and are based on ideas very different from those of modern Western medicine. Most research studies on TCM have focused on specific techniques, primarily acupuncture and Chinese herbal remedies, and there have been many systematic reviews of studies on TCM approaches for various conditions.

However, the use of herbal medicine as a pharmacologic modality in improving several pathological statuses has received attention from medical science researchers. Ginger (*Zingiber officinalis*), a plant that belongs to the *Zingiberaceae* family, is indigenous to Southeast Asia, and for centuries has been an important ingredient in Chinese and Ayurvedic herbal medicines for the treatment of different diseases (Atashak, S., *et al.*, 2014).

Ginger, due to its pungent (spicy) and hot taste, belongs to two of the 19 main groups of Chinese pharmacology, specifically the **Metagroup I – Groups I - IX used to treat acute infections**, that resides in the treatment of the ***extima*** (skin, conduits and mucosa), which contain pores that retain fluids (Greten, H., 2007).

Furthermore, Ginger belongs to the **Group I a) – *Liberantia Extimae Acria et Calida*** as it "*warms the "centre" and the conduits*", being responsible for the upward liberation of the *extima*, supporting the ascending movement of the functional powers to the *extima*, acting primarily on the **Pulmonary Orb** (Po) as the *extima* is activated by this orb. Additionally, this warming drug acts on the nose, part of the Po, which normally tends to ***Algor***

(environmental cold, commonly described by cold skin, stiff muscles, tearing and localised pain with gradual onset). If the pathogenic factor *algor* (the agent) overcomes the outer extimal stage, it enters the intima and may cause deficiencies in several functions, occurring the typical course of an *algor* ("cold") attack, leading to the six stages of the ALT (***Algor Laedens Theory***). In this case, ginger belongs as well to the **Group IX – *Tepefacientia intimae*** (the interior warming drugs), having an effect on functional deficits at the minimum of the regulative sinus curve, at the transition from **Metal** to **Water**, and at the same time, at the beginning of the neutral vector (Greten, H., 2007).

Drugs that warm the interior therefore have a stimulating effect on functions, or in Chinese Medical language, a **suppletive** effect on functional powers, counteracting the symptoms of the phase **Water** (regeneration need, renal signs, in yang deficiency) or insufficiencies of the **Centre** (support of the upward going vector) or even warm the surface (**Metal**). Following this, ginger may act as a rescue of **devastated yang** or **yang deficiency** (a chronic exhaustion condition in which invading cold or infection has reached the interior of the body, seen by the production of excessive calor - **reactive calor**, causing ice-cold feelings combined with an extremely fast pulse, cold limbs and cold sweat) warming the **Earth** channels, as well as influencing several other channels (the *Cardiac*, *Pulmonal*, *Lienal* and *Stomachal* **orbs**).

In Chinese Medicine, ginger's rhizome is often combined with several principles in order to create decoctions that act as *extima* liberating formulations:

- ✓ ***Decoctum ramulorum cassiae***, composed of *ramuli cassiae* (50g), *r. paeoniae albae* (40g), *r. glycyrrhizae tosta* (30g), *rh. zingiberis vir*. (30g) and *fr. jujubae* (4-6), which "*liberates the flesh in algor venti and myalgia*";

- ✓ ***Decoctum parvum draconis viridis***, mainly composed of ***Decoctum ephedrae,*** (*herba ephedrae* (50g), *ramuli cassiae* (40g), *s. armeniacae* (30g) and *r. glycyrrhizae* (10g)), which *"liberates, unfolds, transforms"*, except s. armeniacae and plus *rh. zingiberis*, *r. paeoniae*, *rh. pinelliae praeparata*, *fr. schizandrae* and *c. cinnamomi*, which "*warms the centre when blocked by pituita and algor*" or ***Decoctum magnum draconis viridis*** mainly composed of ***Decoctum ephedrae*** plus *gypsum fibrosum*, *rh. zingiberis* and *fr. jujubae,* which "*liberates the extima, initiates sweat, cools calor, relieves restlessness and malaise, splendor yang*".

Chapter VI – Ginger-drug possible interactions

In literature, few ginger-drug interactions have been reported, since it does not interact with almost any active principle.

Vaes, L. & Chyka, P. (2000), as well as Weidner, M. & Sigwart, K. (2000), admitted no case reports of interactions between ginger and an anticoagulant (warfarin) in rats and humans have been identified to date, which has recently been confirmed by Jiang, X. *et al.* (2006) in an open label randomized study on the effect of four herbal medicines on warfarin pharmacokinetics and anticoagulant response. Regarding ginger, the study was performed in 12 healthy volunteers in 2 clinical trials, who were given 400mg of ginger orally three times per day for one week, before taking a single 25mg-dose of warfarin. The results indicated that ginger does not exert significant effects on either the blood clotting status or pharmacokinetics and dynamics of warfarin.

Still focusing on cardiovascular drugs, Young, H.-Y. *et al*. (2006) have studied the synergistic effect of ginger and an antianginal/antihypertensive drug (nifedipine) on antiplatelet aggregation in healthy human volunteers, as well as hypertensive patients, on a two-phase trial whose results can be seen on Tables 11 and 12.

Table 11 - Synergistic effect of Ginger and Nifedipine on platelet aggregation in normal volunteers.

	Percentage of inhibition of platelet aggregation				
	Nifedipine	Aspirin	Nifedipine + Aspirin	Ginger	Nifedipine + Ginger
Collagen	20.2±0.7	37.2±0.7	82.8±8.5	35.2±0.8	79.8±0.6
ADP	22.6±0.6	39.7±0.8	78.2±9.15	37.8±0.8	75.2±0.8
Epinephrine	23.4±1.0	34.9±0.5	72.2±8.5	35.9±0.7	69.3±0.5

*Collagen, Adenosine Diphosphate (ADP) and Epinephrine as induced drugs for the measurement of platelet aggregation.

Table 12 – Synergistic effect of Ginger, Aspirin and Nifedipine on platelet aggregation in hypertensive patients.

	Percentage of inhibition of platelet aggregation		
	Nifedipine	Nifedipine + Aspirin	Nifedipine + Ginger
Collagen	20.5±0.7	65.2±0.7	64.2±0.5
ADP	22.3±0.6	64.6±1.1	63.8±0.4
Epinephrine	19.2±1.0	62.8±1.1	61.1±0.8

* Collagen, Adenosine Diphosphate (ADP) and Epinephrine as induced drugs for the measurement of platelet aggregation.

The data obtained from the study support that the percentage of platelet aggregation induced by collagen, ADP and epinephrine in hypertensive patients was higher than that in healthy volunteers. Additionally, either aspirin or ginger could potentiate the anti-platelet aggregation effect of Nifedipine both in normal and hypertensive patients, which suggest that ginger and Nifedipine have a synergistic effect on anti-platelet aggregation. Furthermore, they recommended the combination of 1g of ginger with 10mg of nifedipine per day as it would be valuable in cardiovascular and cerebrovascular complication due to platelet aggregation (Young, H.-Y. *et al*., 2006).

Chapter VI - Conclusion

Plant based secondary metabolites, such as plant extracts and essential oils, are widely used in the food industry, and considered as GRAS (Generally Recognised as Safe). Several publications have documented the numerous potential activities of the root extract from *Zingiber officinalis*, and were fully and concisely described on this manuscript.

The papers and journals reviewed provide another example of how it may be possible to explain the action(s) of western medicine in terms of conventional biochemistry and pharmacology. Ginger and many of its chemical constituents have strong properties, and especially, anti-inflammatory actions. As several metabolic diseases and age-related degenerative disorders are closely associated with inflammatory processes in the body, the user of either ginger or one or more of its active compounds as a source of anti-inflammatory to fight inflammation really warrants further attention. Additionally, more studies are also required on the kinetics of ginger and its components, and on the effects of their consumption over a long period of time.

The fourteen-day trial allowed us to know that ginger is almost as effective as a commonly prescribed NSAID for the treatment of muscular pain (ibuprofen). Nevertheless, further trials in humans are required to determine the real efficacy of ginger (or one or more of its compounds) and to establish if there are any adverse effects.

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Appendix

Name: _____

First name: _____

born: _____ Profession: _____

Order of Complaints: Date:

1 _____ VAS

2 _____ VAS

3 _____ VAS

Date:	Date:	Date:
[%] _____	[%] _____	[%] _____
[%] _____	[%] _____	[%] _____
[%] _____	[%] _____	[%] _____

Stool:

Colour: black dark normal yellow white

Consistency: dry normal soft mushy liquid changing, undigested food

Drivenness: (inner tension) +++ ++ + - -- ---

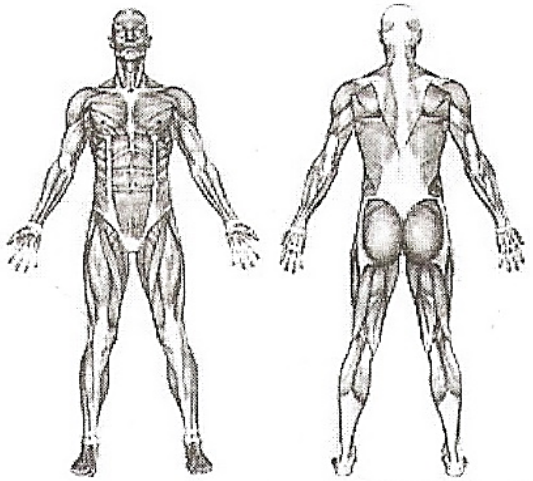
Vol. of urine: 1 glass 2 glasses 3 glasses, conc. normal light

Menses: light dark lumpy flowing too much intermenstrual bleeding fluor

Sperm: much few white yellow opal liquid solid lumpy slimy

Sweat: stinky profuse sticky at night forehead cold hot

Temp. sensation: icy cold sensitive to cold normal warm too warm hot; icy chills cold chills changing



Pharmacotherapy _____ _____ _____

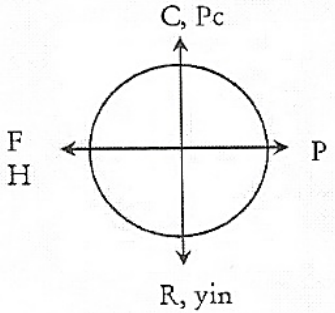
Size: small normal large Colour: pale normal excessively red livid
Structural signs: hairline cracks fissures wadi Vileda freckled red spots
Coating: dry normal clear sticky white yellow brown hyaline
Movement: normal shooting out cannot be held trembling

left	right

left	right

left	right

Constitution:



Agent:

algor: localised, tearing, stiff, better with warmth, worse with cold; hyaline coating; p. intentus

humor: dull, swollen, heavy limbs, sticky coating; p. lubricus

pituita: doughy, lubricous, yellow coating; p. lubricus

ventus: sudden, shooting, tingling, little blisters, paraesthesia; little dots; spasm; p. chordali

ardor: „-itis pain"

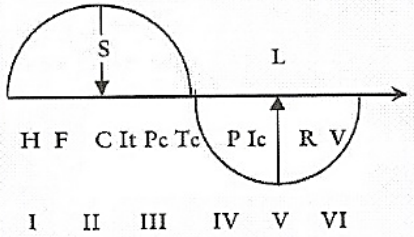
aestus: hot, dizzyness, nausea

ariditas: dry skin, dry cough, worse with the beginning of heating period

xue stasis: heavy stabbing pain, livid tongue

voluptas
pavor
ira - „suppressed" ← cogitatio → maeror solucitudo
timor

Orb: location or pattern



Guiding criteria:

repl.	depl.
calor	algor
extima	intima
yin:	yang:
- yin	- ventus internus
- xue	- ardor vigens
xue deficiency (white gums)	- ascending
- fluids	- disturbed unfolding/ deficiency
- jing	

Treatment concept:

© Greten 10/2010

Complementary Therapy with *Zingiber officinalis* – clinical cases

Clinical sheet answered by patients on days 1, 7 and 14th of the treatment trial (Greten, H. 2010).